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Chapter 22. ALCOHOL

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Contents

22.1 The Control of Excitation and Inhibition

The **glutamate** and **GABA systems** control the intricate balance between excitation and inhibition in the central nervous system. Alterations to this homeostasis can have detrimental effects. Too much excitation leads to anxiety, insomnia, restlessness, exaggerated responses, convulsions and death. Too much inhibition, on the other hand, gives way to sedation, depression, ataxia, anaesthesia, coma and death. Glutamate and GABA are amino acid transmitters, their chemical structures differing by one carboxylic acid group. GABA is synthesized from glutamate via decarboxylation.

Glutamate and GABA act at a variety of receptor subtypes, however only the receptors relevant to the action of alcohol will be discussed here. These include the **$GABA_A$** and **glutamate *N*-methyl-D-aspartate (NMDA) receptors**.

When GABA or its structural analogues bind to the $GABA_A$ receptors, the ligand gated chloride ion channel changes conformation, allowing increased conductance of chloride ions. The equilibrium potential for chloride is close to resting membrane potential, therefore increased chloride conductance stabilises the membrane, thereby reducing membrane excitability.

The glutamate NMDA receptors are similarly significant for their unique properties, they are voltage-dependent ligand-gated ion channels, require binding of the **co-agonist glycine** for activation, are highly permeable to calcium ions, and play an important role in synaptic plasticity.

22.2 Alcohol and its Behavioural Effects

The key ingredient of “alcohol” in alcoholic drinks is **ethanol**. Ethanol is one of the few legal psychoactive drugs.

Behavioural effects of ethanol include myorelaxation, anxiolysis, sedation, impaired cognitive function, and an anticonvulsant effect. At higher doses it can cause motor incoordination, ataxia, amnesia, hypnosis and anaesthesia, and eventually respiratory depression and coma.

22.3 Mechanism of Alcohol Action

Ethanol influences many sites in the central nervous system, including 5-HT and glycine receptors, and G protein-coupled inwardly rectifying K^+ (GIRK) channels. However it appears its major sites of action at low to moderate doses are $GABA_A$ receptors, and NMDA receptors at higher doses. At $GABA_A$ receptors it enhanceS GABA activation, by increasing the mean ion channel open time and facilitating GABA binding. At NMDA receptors it appears to act as a non-competitive inhibitor. Thus ethanol can **reduce excitation** and **increase inhibition** in the brain, leading to over-inhibition.

Although $GABA_A$ receptors are ubiquitously (widely) distributed throughout the CNS, the location of $GABA_A$ receptors modulated by ethanol is significant. Receptors in the cerebellum likely contribute to the impaired motor coordination and ataxia induced by ethanol. Receptors in specific thalamic nuclei may mediate some sedative, hypnotic and anaesthetic effects, while those in the hippocampus, amygdala and neocortical regions contribute to the cognitive impairment, anxiolysis and amnesia.

22.4 General Considerations with the use of Alcohol.

As with many drugs acting on GABA receptors, **sex differences** occur with ethanol. Men are less sensitive to the intoxicating effects of ethanol than women, and driving regulations and drinking guidelines reflect this notable sex difference. For example, men are advised to drink no more than two standard drinks in the first hour to avoid going over the legal blood alcohol concentration (BAC) limit of 0.05%, while women are advised that more than one standard drink per hour will tip them over the limit. Studies have suggested that the sex differences may partly be due to the difference in ethanol's ability to induce neurosteroid synthesis in the CNS.

Another important consideration with the use of alcohol is **drug-drug interactions**. Given the numerous sedative, anxiolytic and hypnotic substances acting on $GABA_A$ receptors, combinations of these drugs with ethanol are dangerous, and have been exploited to induce amnesia and sedation in some social settings.

Finally, complications arising from the **metabolism of ethanol** must be considered in some populations. Ethanol is oxidised in the first instance via alcohol dehydrogenase (and at high doses, CYP2E1) to acetaldehyde, a highly toxic and unstable compound. Regular heavy consumption of ethanol during pregnancy has been shown to lead to birth defects, and one mechanism thought to be involved is via the toxic action of acetaldehyde on the developing embryo and foetus.

Acetaldehyde is further synthesized via mitochondrial acetaldehyde dehydrogenase to acetic acid. Individuals lacking the mitochondrial form of acetaldehyde dehydrogenase, relatively common in some Asian populations, may experience increased intoxication. Moreover, acetic acid is metabolized to acetyl CoA then to fatty acids in the liver. Prolonged overconsumption of alcohol may increase fatty acid synthesis in the liver, leading to steatosis.

22.5 Long-term Adaptive Changes with the use of Alcohol

Prolonged use of ethanol alters the balance of neuronal excitation and inhibition, and appears to cause adaptive changes in nervous system function. Chronic intermittent or heavy prolonged usage can lead to adaptive changes in the brain, including changes in $GABA_A$ receptor expression and subunit reshuffling. Such changes in expression and subunit reshuffling substantially alter the pharmacological properties of $GABA_A$ receptors, with important functional consequences.

Long-term use of ethanol may lead to **tolerance**, such that higher doses are required to produce the same effect, and **dependence**, manifesting as cravings for the substance, and a physical withdrawal syndrome. The dose required and period of usage to elicit dependence, however, may vary between individuals. The rewarding effects of ethanol may arise from its action at $GABA_A$ receptors in the ventral tegmental area and nucleus accumbens of the dopamine mesolimbic "reward/motivational salience" pathway. Mood state also impacts upon dependence, and alcohol use disorders are more common in sufferers of anxiety and depression. There is also evidence of genetic susceptibility to alcohol dependence, and several candidate genes have been identified including genes encoding GABA receptors.

The **alcohol withdrawal syndrome** manifests as insomnia and sleep disturbances, anxiety, hyperexcitability, delirium tremens, hyperalgesia, and lowered seizure threshold (increased risk of seizures), and can be treated with **benzodiazepines**.